REMARKS

Claims 35, 36, 38, and 39 stand objected to as reciting non-elected subject matter. By way of the above amendment, has either canceled or amended the claims so as to overcome this objection.

Claims 1-7, 25, 26, and 28-29 stand rejected under 35 USC §101 as directed to non-statutory subject matter. Applicant acknowledges the Examiner's suggestion that the claims may be amended to "an isolated and purified peptide". Applicant has instead amended the claims to set forth that the claimed invention is directed to a "genetically engineered fluorescent protein". Applicant respectfully submits that the claim amendment traverses the §101 rejection. In addition, the claim language is consistent with the needed scope of Applicant's claim in that the claimed protein has utility as a biosensor and may be present within living cells. As such, limitation to "an isolated or purified protein" is inaccurate with respect to the claimed protein being present within a living cell.

Claims 1-7, 25, 26, and 28-29 are rejected under 35 USC §112 first paragraph. The Examiner has made a new matter rejection based upon language added during the prior amendment. By way of the above amendment, Applicant respectfully submits that the claims now set forth structural limitations with respect to a cleavage site which are fully supported by Applicant's specification and claims as originally filed. In particular, Applicant refers the Examiner to the example set forth on page 10 of Applicant's specification as well as the disclosure on page 9, last full paragraph, which sets forth β-sheet loop structures present within green fluorescent protein along with a variety of other fluorescent proteins.

Applicant respectfully disagrees with the Examiner's comments that Applicant's specification requires one to experimentally deduce x-ray structure determination for suitable crystals. As set forth in Applicant's specification, Applicant relied upon published literature reports which identified the β-sheet structures known for green fluorescent proteins. Applicant has further identified, within both the original specification and in the prior response (paper 13), published literature reports which provide information on β-sheet structures for other fluorescent proteins.

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Applicant's methodology provides for insertion techniques and subsequent evaluation for a single fluorescent protein which are compatible with a wide number of β-sheet containing fluorescent proteins. No undue experimentation is needed in order to evaluate suitable protease insertion sites from the limited number of adjacent β-sheets in various fluorescent proteins. Accordingly, Applicant respectfully submits that Applicant's claim 1 does not need to be limited to the specific fluorescent protein having SEQ ID NO: 41. Applicant has identified other green fluorescent proteins having different sequences which are enabled by Applicant's specification. Additionally, Applicant has identified methodology and examples which allow for a straightforward application to other fluorescent proteins which the literature reports have similar β-sheet pair morphology.

In summary, Applicant respectfully submits that the Examiner's impression that experimentation of growing single crystals and conducting x-ray diffraction are requirements for carrying out Applicant's invention are misplaced. The published literature, as cited in both Applicant's specification as well as in Applicant's prior response, sets forth that the necessary structures for protease insertion are known for a wide variety of fluorescent proteins other than green fluorescent proteins.

Claims 1, 2, 25, 26, 28, 29, and 34 stand rejected under USC 35 §102(b) as being anticipated by Xu et al. Applicant respectfully submits that Applicant's claims are not anticipated by this reference. Applicant's claims are directed to an inserted cleavage site within a single fluorescent protein molecule. The Xu et al reference is directed to two different fluorescent proteins which are joined together by a capase-3 cleavage site. (See Xu et al abstract.) In contrast, Applicant's claimed invention is directed to an insertion of a cleavage site within a single fluorescent protein molecule. The insertion site is not used to link two different fluorescent protein molecules as provided by Xu et al.

To the extent the teachings in Xu et al are directed to fluorescent energy transfer from a green fluorescent protein to an adjacent blue fluorescent protein, the Xu et al reference does not anticipate nor suggest insertion of a protease cleavage site within a single fluorescent protein. The detection method of Xu et al and the methodology

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therein is designed around a change of energy transfer between two fluorescent molecules. In contrast, Applicant's present invention requires but a single fluorescent molecule having a cleavage site inserted within the fluorescent protein itself.

Inasmuch as all outstanding issues raised by the Examiner have been addressed, it is respectfully submitted that the present application is in condition for allowance, and action to such effect is earnestly solicited. The Examiner is encouraged to telephone the undersigned at his/her convenience should only minor issues remain after consideration of the present Amendment, to permit early resolution of same.

Please charge any additional fees required by this Amendment to Deposit Account No. 04-1403.

Respectfully submitted,

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MARKED UP CLAIMS COPY

1 (Twice Amended) A genetically engineered fluorescent protein comprising [an 11-stranded β-barrel formed from 11 β-sheets surrounding a chromophore-containing co-axial α-helix, each of said β-sheets forming said β-barrel being joined by a loop structure to at least one other adjacent β-sheet forming said β-barrel modified such that said modified] a fluorescent protein which incorporates by insertion a [cleavage site for a] protease cleavage site into a single fluorescent protein, cleavage of said [modified] fluorescent protein at said cleavage site by [said] a protease causing the alteration of at least one of [the] an emission and an excitation spectra of said [modified] fluorescent protein.

3. (Amended) A fluorescent protein according to claim 2, said [modified] fluorescent protein having said cleavage site [incorporated in the loop structure joining] inserted between any pair of adjacent β-sheets of a loop structure of said green fluorescent protein.

4. (Twice Amended) A fluorescent protein according to claim 3, wherein said pair of adjacent β-sheets [being] are selected from the group consisting of β-sheet pairs numbers 9 and 10, 5 and 6, and 8 and 9.

5. (Twice Amended) A fluorescent protein according to claim 3, said [modified] fluorescent protein having SEQ. ID NO: 41.

6. (Twice Amended) A fluorescent protein according to claim 1, [being] wherein said single fluorescent protein is selected from [any one of] the group consisting of a blue fluorescent protein, a cyan fluorescent protein, a yellow fluorescent protein, and a DsRed fluorescent protein.

26. (Amended) A fluorescent protein according to claim 25, said caspase being selected from [any one of] the group consisting of caspase-3, caspase-6, caspase 7, caspase-8 and caspase-9.

28. (Amended) A genetically engineered [modified] fluorescent protein comprising:

a green fluorescent protein having a loop structure, said loop structure having incorporated therein a protease cleaving site, said loop structure positioned between a first β sheet of said fluorescent protein and a second β sheet of said fluorescent protein adjacent to said first β sheet wherein cleavage

MARKED UP CLAIMS COPY

of said fluorescent protein at said cleavage site alters at least one of an emission spectra and an excitation spectra of said [modified] fluorescent protein.

36. (Amended) A fluorescent protein according to claim 1 wherein said cleavage site has a sequence of [any one of the group consisting of] SEQ. ID NO[s]: [7-13] 4.